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(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number  
**WO 2004/000273 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 9/107**,  
31/216, 31/235, 31/407, 31/426, 31/44, 31/4164, 31/4709

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(21) International Application Number:  
PCT/EP2003/006496

(22) International Filing Date: 20 June 2003 (20.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
MI2002A001392 25 June 2002 (25.06.2002) IT

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,  
SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG,  
US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

— *with international search report*  
— *before the expiration of the time limit for amending the  
claims and to be republished in the event of receipt of  
amendments*

*For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.*

(54) Title: ORAL PHARMACEUTICAL FORMS OF LIQUID DRUGS HAVING IMPROVED BIOAVAILABILITY

(57) Abstract: The present invention relates to new pharmaceutical compositions for the administration of liquid drugs in solid oral forms, said compositions comprising one or more active ingredients, one or more surface-active agents and optionally a co-surfactant and/or an absorption enhancer absorbed on a solid inert carrier.



WO 2004/000273 A1

## TITLE OF THE INVENTION

"ORAL PHARMACEUTICAL FORMS OF LIQUID DRUGS HAVING IMPROVED BIOAVAILABILITY"

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The present invention relates to new pharmaceutical compositions for the administration of liquid drugs in solid oral forms, said compositions comprising one or more active ingredients, one or more surface-active agents and optionally a co-surfactant and/or an absorption enhancer absorbed on a solid inert carrier.

It is well known in the art that it is difficult to orally administer drugs, which are liquid at room temperature. Generally, these drugs show a poor water solubility and therefore a limited absorption, resulting in a poor bioavailability together with an absorption characterized by a strong inter- and intra-subject variability. Therefore, it would be important to have at disposal compositions able to improve these characteristics that could seriously compromise the bioavailability as well as the therapeutic activity of said compounds.

Generally, oily drugs are formulated in soft or hard gelatine capsules which present technical problems relating to filling, losses etc. They can be also absorbed on inert carriers, but in this case even though the technological problems can be solved, it is impossible to improve the bioavailability.

In WO 01/66087 and WO 01/66088 pharmaceutical compositions for oral administration of a liquid active ingredient, for example a nitrooxyderivative of naproxen or other NSAIDs, are disclosed. Said compositions comprise, further to the active ingredient, one or more surfactants, optionally an oily or semi-solid fat or one or more short-

chain alcohols. These compositions form an oil-in-water emulsion in situ upon contact with aqueous media such as gastrointestinal fluids.

In WO 95/08983 a self-emulsifying composition suitable  
5 for oral administration is disclosed, said composition forming a microemulsion in situ upon contact with biological fluids. The described composition comprises an active ingredient, a lipophilic phase consisting of a mixture of glycerides and fatty acids esters, a surface-  
10 active agent, a co-surfactant and a hydrophilic phase consisting of the gastrointestinal fluids.

In EP 274 870 a pharmaceutical composition containing a non-steroidal anti-inflammatory drug (NSAID) and a surfactant is described, said composition being able to  
15 form micelles containing said active ingredient upon oral administration

In WO 01/41737 an immediate-release solid oral pharmaceutical composition, comprising a solid carrier and a liquid drug or a solution of a poor soluble drug, is  
20 described.

It has been now surprisingly found that it is possible to improve the oral bioavailability of liquid drugs at room temperature, by formulating the solid drug in solid pharmaceutical compositions able to form emulsions in situ  
25 upon contact with the biological fluids and with the water used for ingesting the pharmaceutical form.

In particular, the present invention relates to the preparation of solid pharmaceutical compositions for oral administration consisting of an admixture absorbed in a  
30 solid inert carrier, said admixture comprising:

- i) one or more liquid active ingredients and
- ii) one or more surfactants and
- iii) optionally a co-surfactant and/or

iv) optionally an absorption enhancer  
said composition forming an oil-in-water emulsion upon  
contact with aqueous media such as biological fluids.  
Particularly preferred is a pharmaceutical composition  
5 according to claim 1 wherein the admixture absorbed in the  
inert carrier comprises:

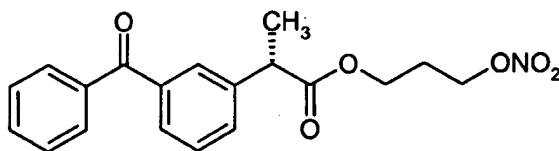
- i) one or more liquid active ingredients;
- ii) one or more surfactants;
- iii) an absorption enhancer

10

For liquid active ingredient, a drug being liquid,  
generally oily, at room temperature is meant. Examples of  
drugs being oily liquids at room temperature are for  
example several nitrate esters of drugs such as the non-  
15 steroidal anti-inflammatory drugs (NSAIDs) described in EP  
609415, EP 670825, EP 722434, EP 759899 and patent  
applications WO 00/51988, WO 00/61537, WO 00/61541 e WO  
01/54691 in the name of applicant.

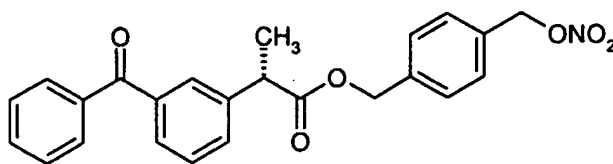
Examples of said nitrate esters are the following:

- 20 (S)-3-benzoyl- $\alpha$ -methylbenzeneacetic acid 3-  
(nitrooxy)propyl ester



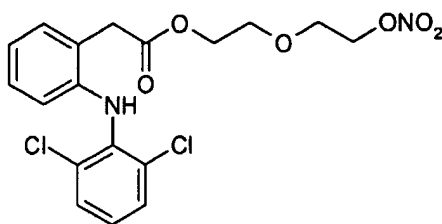
(I)

- (S)-3-benzoyl- $\alpha$ -methylbenzeneacetic acid 4-  
25 (nitrooxymethyl)phenyl-methyl ester



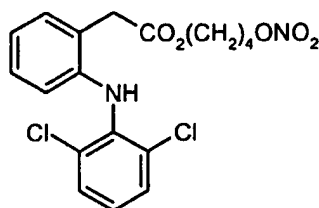
(II)

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 5-  
(nitrooxy)ethyl-oxyethyl ester



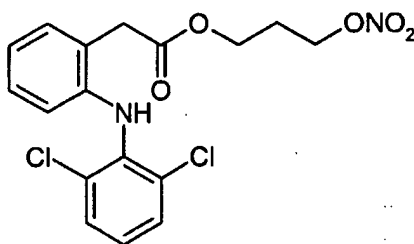
(III)

5 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 4-  
(nitrooxy)butyl ester (NO-Diclofenac)



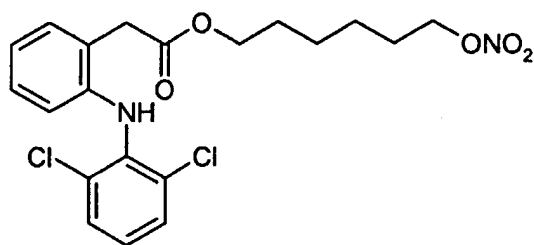
(IV)

2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid 3-  
10 (nitrooxy)propyl ester



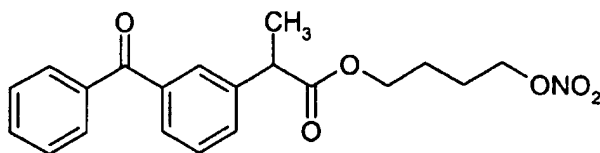
(V)

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 6-  
(nitrooxy)hexyl ester



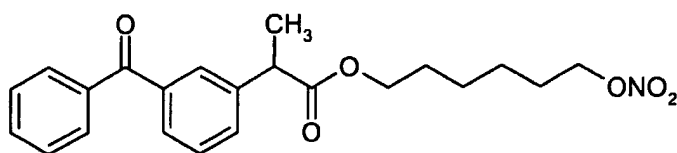
(VI)

3-benzoyl- $\alpha$ -methylbenzeneacetic acid 4-(nitrooxy)butyl ester



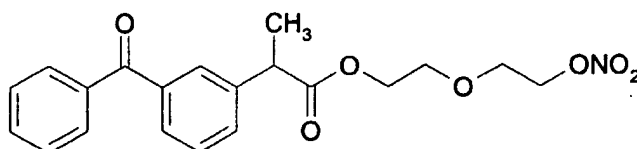
(VII)

5 3-benzoyl- $\alpha$ -methylbenzeneacetic acid 6-(nitrooxy)hexyl ester



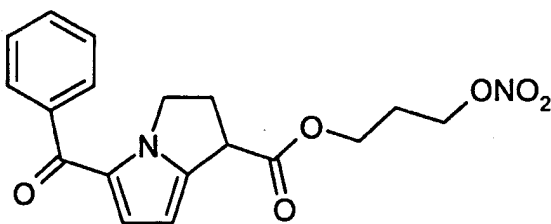
(VIII)

3-benzoyl- $\alpha$ -methylbenzeneacetic acid 5-(nitrooxy)ethoxyethyl ester



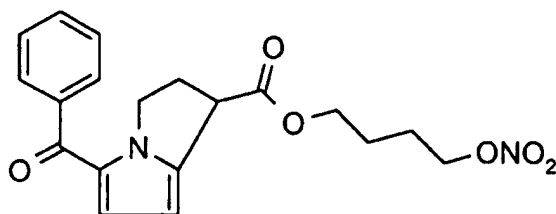
(IX)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 3-(nitrooxy)propyl ester



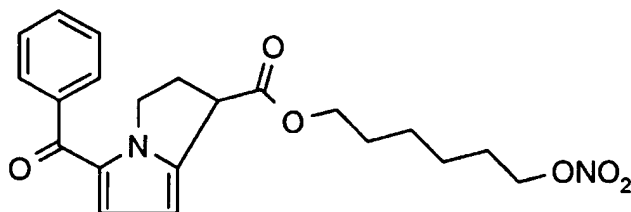
(X)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-(nitrooxy)butyl ester



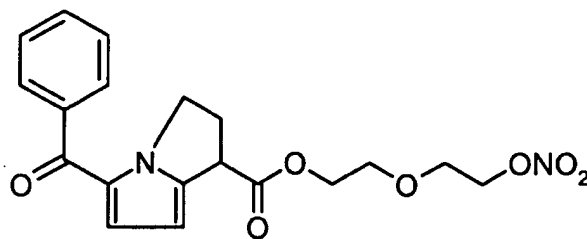
(XI)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 6-(nitrooxy)hexyl ester



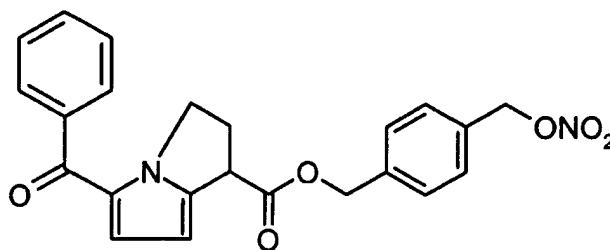
(XII)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 5-(nitrooxy)ethyl-oxyethyl ester



(XIII)

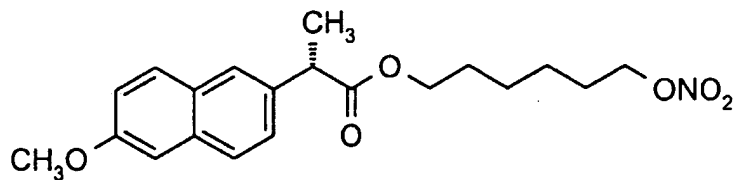
5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-(nitrooxymethyl)-phenylmethyl ester



(XIV)

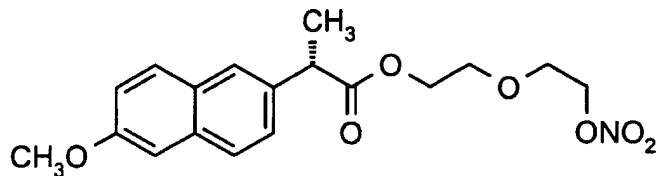
15 (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 6-(nitrooxy)hexyl ester





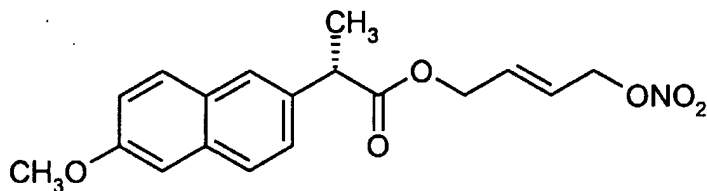
(XV)

(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 5-(nitrooxy)ethyl-oxyethyl ester



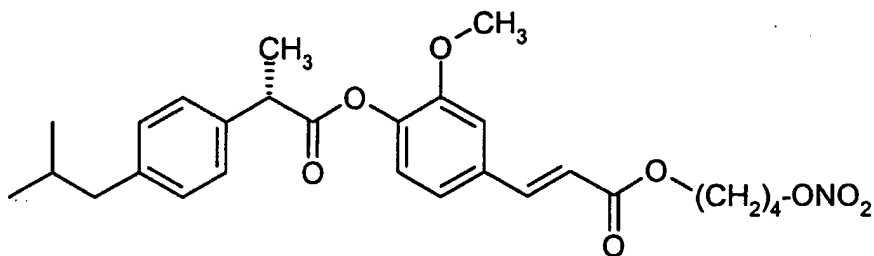
(XVI)

(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 4-nitrooxy-2-butenyl ester



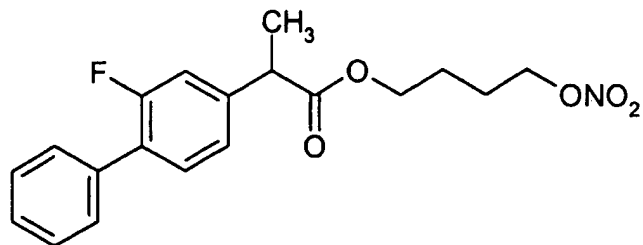
(XVII)

trans-3-[4-[ $\alpha$ -methyl-4-(2-methylpropyl)benzene]acetyloxy]-3-methoxy-phenyl]-2-propenoic acid 4-(nitrooxy)butyl ester



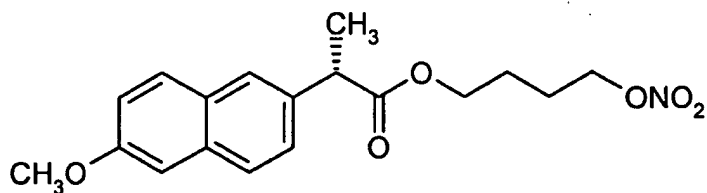
(XVIII)

2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 4-(nitrooxy)butyl ester (NO-Flurbiprofen)



(XIX)

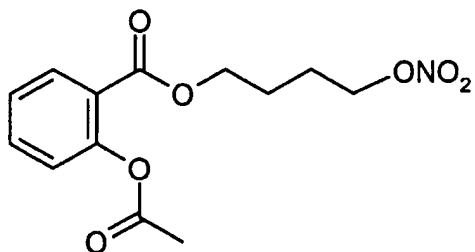
(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 4-(nitrooxy)butyl ester (NO-Naproxen)



5

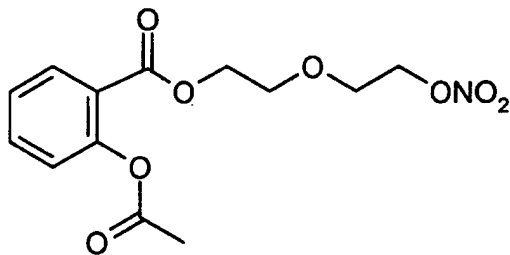
(XX)

2-(acetyloxy)benzoic acid 4-(nitrooxy)butyl ester



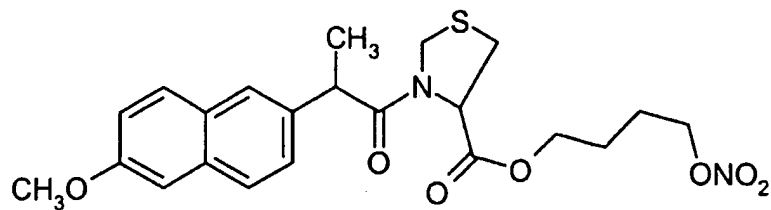
(XXI)

10 2-(acetyloxy)benzoic acid 5-(nitrooxy)ethoxyethyl ester



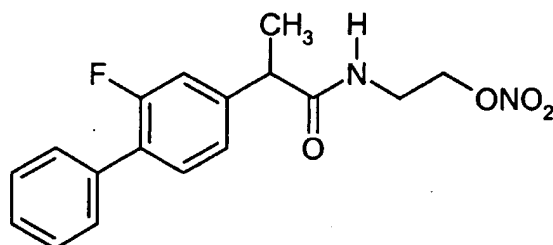
(XXII)

3-(6-methoxy- $\alpha$ -methyl-2-naphthaleneacetyl)-thiazolidine-4-carboxylic acid 4-(nitrooxy)-butyl ester



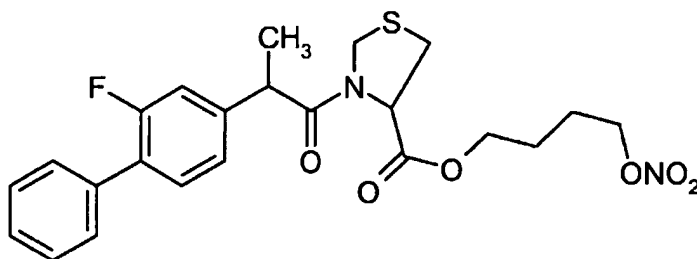
(XXIII)

N-(2-nitrooxyethyl)-2-fluoro- $\alpha$ -methyl[1,1'-biphenyl]-4-acetamide



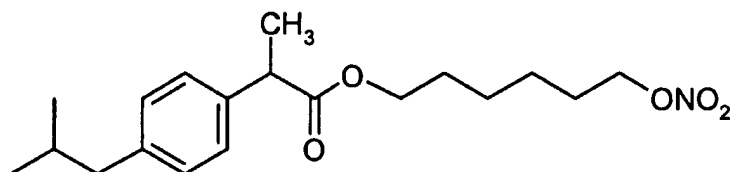
(XXIV)

3-[2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetyl]-thiazolidine-4-carboxylic acid 4-(nitrooxy)butyl ester



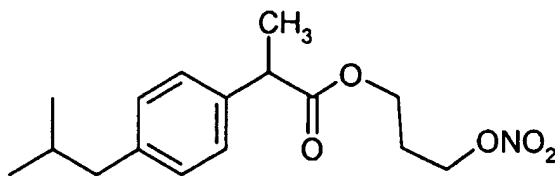
(XXV)

$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 6-(nitrooxy)hexyl ester



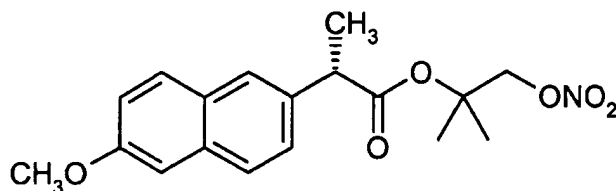
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$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 3-(nitrooxy)propyl ester



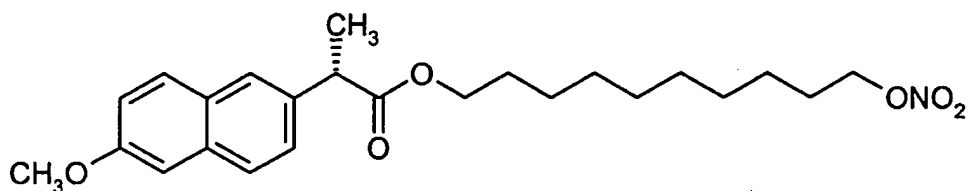
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(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 1-nitrooxy-2-methyl-2-propyl ester



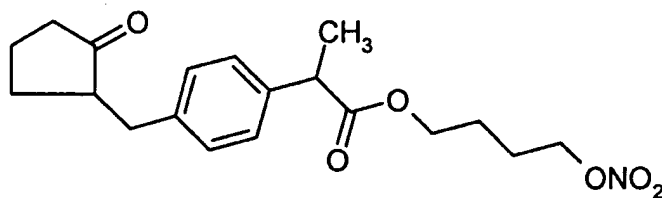
(XXVIII)

(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 10-(nitrooxy)decyl ester



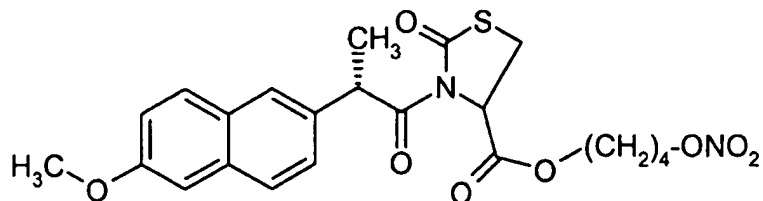
(XXIX)

$\alpha$ -methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid 4-(nitrooxy)-butyl ester



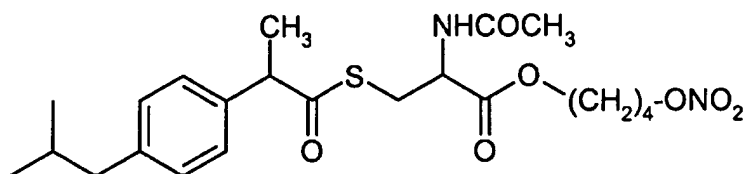
(XXX)

3-(6-methoxy- $\alpha$ -methyl-2-naphthaleneacetyl)-R(-)-2-oxothiazolidine-4-carboxylic acid 4-(nitrooxy)butyl ester



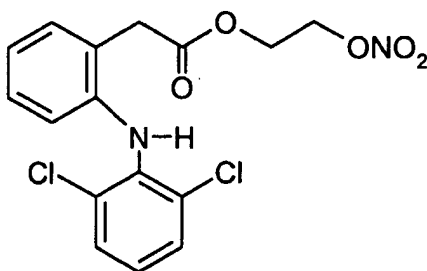
(XXXI)

(S) -N-acetyl- [ $\alpha$ -methyl-4-(2-methylpropyl)benzene-acetyl] -  
cysteine 4-(nitrooxy)butyl ester



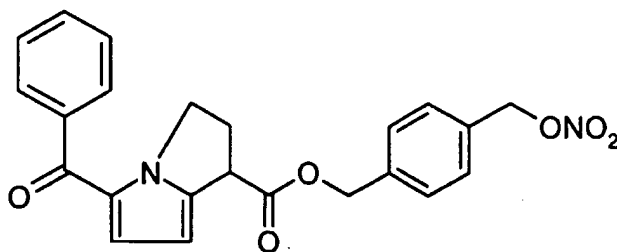
(XXXII)

2-[2,6-dichlorophenyl)amino]benzeneacetic acid 2-  
(nitrooxy)ethyl ester



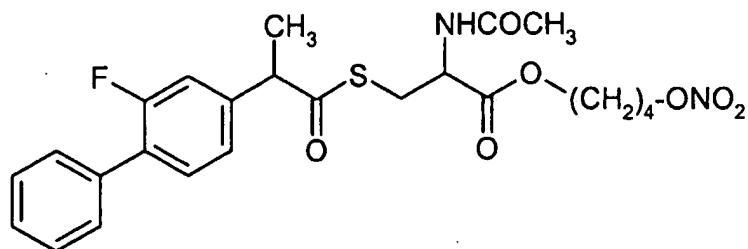
(XXXIII)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-  
(nitrooxy-methyl)phenylmethyl ester



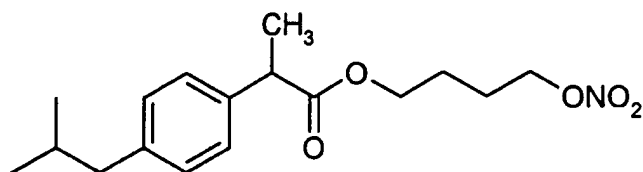
(XXXIV)

(S) -N-acetyl- [2-fluoro- $\alpha$ -methyl (1,1'-biphenyl) -4-  
acetyl]cysteine 4-(nitrooxy)butyl ester



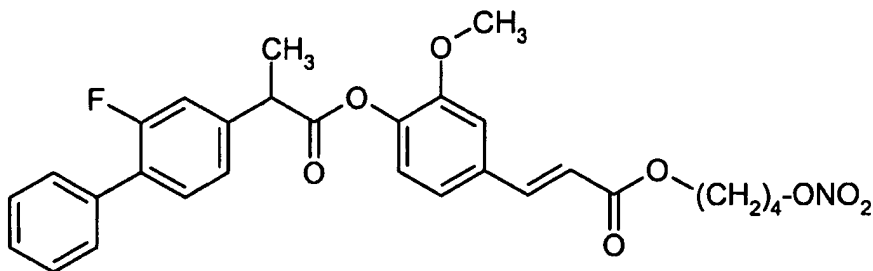
(XXXV)

$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 4-(nitrooxy)butyl ester



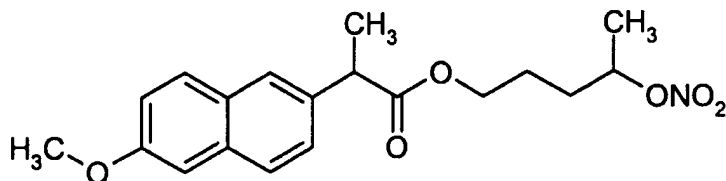
(XXXVI)

trans-3-[4-[2-fluoro- $\alpha$ -methyl(1,1'-biphenyl)-4-acetyloxy]-3-methoxy-phenyl]-2-propenoic acid 4-(nitrooxy)butyl ester



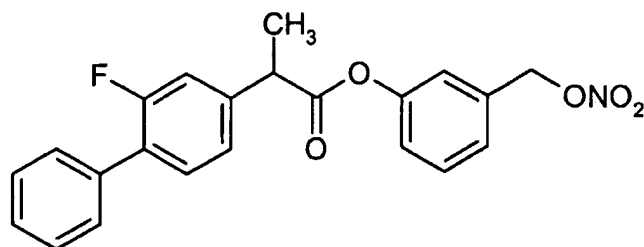
(XXXVII)

(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 4-(nitrooxy)-4-methylbutyl ester



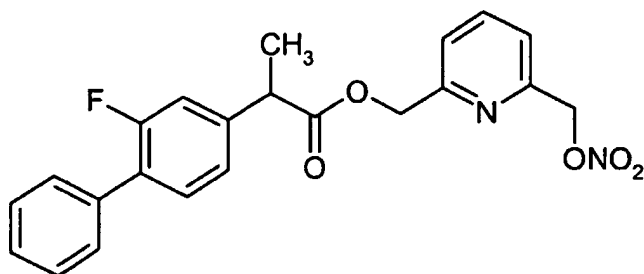
(XXXVIII)

2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 3-(nitrooxymethyl)phenyl ester



(XXXIX)

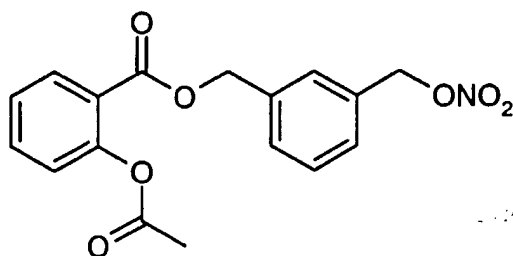
2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 6-  
(nitrooxymethyl)-2-methylpyridyl ester



5

(XL)

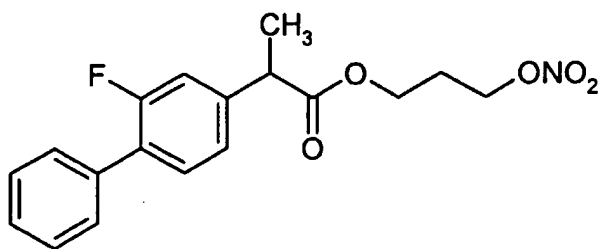
2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)-methylphenyl  
ester



10

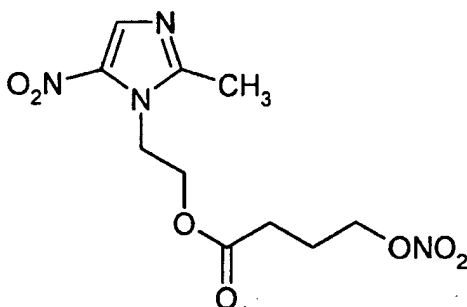
(XLI)

2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 3-  
(nitrooxy)propyl ester



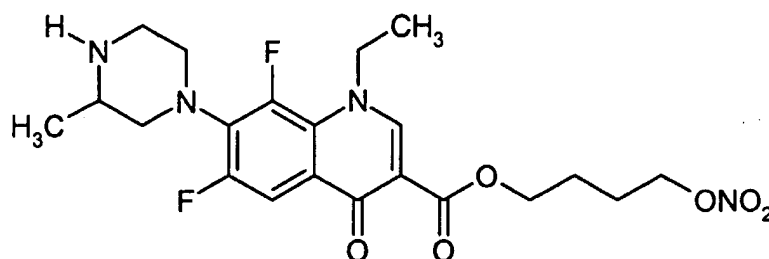
(XLII)

4-(nitrooxy)butanoic acid 2-methyl-5-nitroimidazole-1-ethyl ester



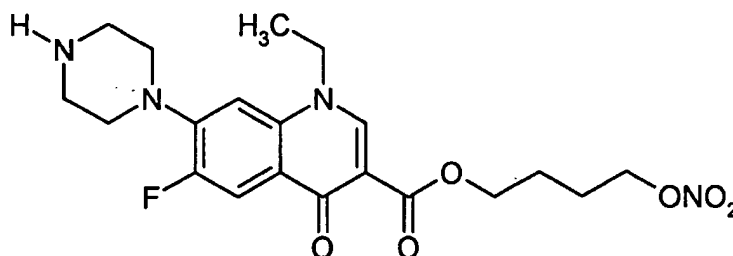
(XLIII)

5 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid 4-(nitrooxy)butyl ester



(XLIV)

10 Norfloxacin 4-(nitrooxy)butyl ester



(XLV)

15 Further examples of liquid drugs are nicotine, nitroglycerin, valproic acid, benzonatate, clofibrate, clorfeniramine, clorfenoxamine, clorfentermine and clorpromazine and liquid vitamins.



The compositions of the invention are able to form an emulsion, upon ingestion of the pharmaceutical form by a patient, having reduced droplet size. The average droplet size of the emulsion is of from 0.1 and 50 microns and preferably is less than 5 micron.

The emulsion droplet size is measured by simulating the formation of an emulsion by adding in a beaker 50 ml of a 0.1N HCl aqueous solution and 100 mg of the composition under examination. The time required for the mixture to form an emulsion, can vary from 20 seconds to 10 minutes depending on the composition. The average droplet size of the emulsion was then determined by employing the light scattering technique or electronic microscopy.

Examples of surfactants that can be employed are anionic, non-ionic and cationic surfactants. Examples thereof may include, but are not limited to, alkaline soaps, such as sodium and potassium stearate, organic amines soaps, sulphuric esters, such as sodium lauryl sulphate, monolauryl glycerosulphuric acid sodium salt, alkyl aryl sulfonates, esters and ethers of polyethylene glycols, polysorbates, benzalkonium chloride, cetyltrimethylammonium bromide, cetrimide, particularly the commercially available products Arlacel, Tween, Capmul, Cremophor, Labrafac, Labrafil, Labrasol, etc. In a few cases it can be useful to add also co-surfactants, that is when a well definite HLB (hydrophilic-lipophilic balance) is requested. Preferred co-surfactants are straight or branched chain alcohols, preferably C<sub>1</sub>-C<sub>6</sub> alcohols, such as ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, and polyols such as glycerol, ethylene glycol, propylene glycol, isopropylene glycol, butylene glycol, isobutylene glycol.

In order to improve the absorption, an absorption enhancer can be added to the active ingredient, dissolved or suspended in the surface-active agent and optionally in the co-surfactant. Many substances possess said activity and among these the following can be mentioned: polysorbates, sorbitan esters, sodium dioctyl sulfosuccinate, ethoxydiglycol, ethoxylated nonyl phenols, polyethylene lauryl ether, phospholipid derivatives, fatty acid esters, biliary acid derivatives, aprotic solvents such as dimethyl sulfoxide, dimethylformamide, dimethylacetamide and 2-pyrrolidone.

The active ingredient, surfactants and absorption enhancer admixture is allowed to absorb on an inert carrier in such a ratio to obtain a powder having good technological characteristics as far as for example free-flowing is concerned. For the absorption of said mixture generally granulators, kneaders or mixers normally used in the pharmaceutical field can be employed. Generally the mixture/solid carrier ratio may vary from 1:20 to 10:1 even though the preferred ratio is from 1:2 to 2:1.

As solid carrier any non toxic pharmaceutical compound may be used, including for example clays such as bentonite, kaolin, silica derivatives such as Aerosil, Cabosil, cellulose derivatives such as Avicel, silicates such as magnesium trisilicate, talc, hydroxides such as magnesium and aluminium hydroxide, starches, sugars and cyclodextrins. Silica is the preferred absorber.

The ratio by weight of active ingredient:surfactant may vary from 1:0.1 to 1:10, preferably of from 1:0.3 to 1:3.

The ratio by weight of co-surfactant:surfactant may vary from 1:0.1 to 1:5, preferably of from 1:0.1 to 1:5.

The ratio by weight of absorption enhancer:surfactant may vary from 1:0.1 to 1:10, preferably of from 1:0.3 to 1:3.

The ratio by weight of admixture : solid carrier may vary from 1:20 to 10:1, preferably of from 1:2 to 2:1.

The resulting product is a free-flowing powder that can be employed in several pharmaceutical forms in the form for example of sachet), tablets (chewing, effervescent or quick dissolution tablets), controlled release capsules or tablets so as to have the active ingredient release in particular areas of the gastrointestinal tract; for this purpose, the coating will be gastroresistant or specifically directed into gut areas, for example colon.

Depending on the pharmaceutical form type, it is possible to use suitable excipients for having the desired formulation. Thus in the case of sachets, sugars, suspending agents, flavourings and sweeteners can be employed, whereas for tablets and capsules, diluents, disintegrants and lubricants can be used. Examples for these materials can be found in Remington's Pharmaceutical Sciences, 17th Edition, Mack Publishing Company, Easton, Pa., 1985.

20

### EXAMPLES

#### Example 1

Preparation of 2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid 4-(nitrooxy)butyl ester (NO-diclofenac; formula (IV)) adsorbed on colloidal silica

25	Compound of formula (IV)	100 g
	Cremophor EL	50 g
	Phospholipon 80 H	50 g
	Aerosil 200	100 g
	Explotab	100 g

30 Cremophor EL and compound of formula IV were added in a suitable vessel and mixed to homogeneity. In the same time Aerosil 200, Phospholipon 80 H and Explotab were mixed separately. The powder mixture was slowly introduced in a

mixer under stirring until complete absorption of the components was achieved. Emulsion average droplet size: 2,2 micron (minimum 0,27, maximum 13,3).

## 5 Example 2

Preparation of a pharmaceutical powder form (sachet) for oral use employing the active ingredient mixture of Example 1

	Mixture of Example 1	400 g
10	Orange aroma powder	150 g
	Lemmon aroma	50 g
	Saccharin sodium	10 g
	Saccharose	2390 g

For preparing sachets, NO-diclofenac absorbed as described in Example 1 was mixed adding orange and lemon flavour as well as saccharin sodium and saccharose. A cube mixer was used with stirring at 9 rpm for 15 minutes. The mixture was distributed in sachets each weighing 3,0 g.

### Dissolution test

20 On the mixture obtained as described in Example 2, a dissolution test was carried out in 0.1N HCl at 37°C with a rotation speed of 50 rpm. The dissolution results are listed in Table 1.

TABLE 1

	NO-diclofenac absorbed on Aerosil 200 (without forming an emulsion)	Composition of the invention (example 2)
Time	% dissolved	% dissolved
0	0	0
15	3,4	88,7
30	4,8	90,2
60	5,7	93,2

**Example 3**

Preparation of 2-fluoro- $\alpha$ -methyl(1,1'-biphenyl)-4-acetic acid 4-(nitrooxy)butyl ester (NO-flurbiprofen; formula (XIX)) absorbed on colloidal silica

5	NO-flurbiprofen	406 g
	Cremophor EL	106 g
	Aerosil 200	300 g
	Explotab	200 g

A suitable vessel was charged with NO-flurbiprofen and  
10 Cremophor EL and the mixture was stirred until a homogenous product was obtained. Separately, Aerosil 200 was mixed with Explotab and the whole was added to the previous mixture to give a homogenous mixture that was poured on a 0,85 mm sieve.

15 Average emulsion droplet size: 1.5 micron (minimum 0,20; maximum 12,8).

**Example 3.1**

Preparation of a pharmaceutical powder form for oral  
20 use (sachets) employing the active ingredient mixture obtained in example 3

	Mixture of example 3	1000 g
	Saccharin sodium	20 g
	Orange aroma	300 g
25	Saccharose	4674 g

For preparing 3 g sachets, each containing 200 mg of active ingredient, 1000 g of the mixture obtained as previously described in example 3 were mixed with saccharin sodium, orange aroma and saccharose.

30

**Example 3.2**

Preparation of tablets employing the mixture of example 3.

Mixture of example 3      500 g  
PVP K30                      20 g  
Avicel pH 102               277 g

PVP K 30 was dissolved in 300 g water and the solution  
5 was used to wet the mixture of example 3 in a Erweka mixer.  
The product thus obtained was poured on a 2 mm sieve and  
then it was dried in an oven at 40°C for 3 hours.  
Afterwards, it was poured on a 1 mm sieve in a floating  
granulator and Avicel was added under stirring in a V mixer  
10 for 15 minutes. The product was compressed to the  
theoretical weight of 800 mg with a 18x10 mm oblong punch.  
Tablets having the following characteristics were obtained:  
Title of a.i. NO-flurbiprofen: 201.3 mg/cpr  
Hardness: 4 Kp  
15 Friability: < 0.1%  
Disgregation time: 4 min

#### Example 4

Preparation of a solid pharmaceutical form (granulate)  
20 using (S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 4-  
(nitrooxy)butyl ester (NO-Naproxen; compound of formula  
(XX)).

NO-Naproxen                100 mg  
Tween 80                    50 mg  
25 Phospholipon 80 H      50 mg  
Aerosil 200                100 mg  
Explotab                    100 mg

100 mg of Phospholipon 80H were dispersed in 2,5 ml  
water by heating at 85°C. The dispersion of Phospholipon 80  
30 H was added under stirring to a mixture of NO-Naproxen and  
Tween 80. After adding Phospholipon, Aerosil and Explotab  
were added under stirring. A granulate was obtained and  
dried in an oven. The granulate was sieved through a 600  $\mu$ m

sieve. By dispersing 400 mg of this granulate in 20 ml water, an emulsion having an average droplet size of 2.2 micron was obtained (minimum 0.27; maximum 13.3).

#### 5 Example 5

Preparation of coated tablets employing the tablets obtained as described in example 3.2

	NO-Flurbiprofen tablets of ex. 3.2	800 g
	Methocel E15	150 g
10	Titanium dioxide	20 g
	Talc	20 g
	PEG 600	30 g
	96% alcohol	1600 g

Methocel E 15 and PEG 6000 were dissolved in a suitable vessel and then talc and titanium dioxide were dispersed therein. The tablets prepared as described in example 3.2 were charged in a Pellegrini vessel and the tablet coating was performed with the film forming suspension according to the following parameters:

20	Air entry: 60°C (300 mc <sup>3</sup> /h)
	Suction: 0,4 mc <sup>3</sup> /h
	Drum rotation: 4 r/m
	Film forming solution range: 30 ml/min

#### 25 Example 6

Preparation of gastroresistant coated tablets employing the tablets obtained as described in example 3.2

	Tablets prepared according to example 3.2	19 kg
	Eudragit E 30 D	0.49 kg
30	Talc	0.19 kg
	Triethyl citrate	0.05 kg
	Titanium dioxide	0.05 kg
	Silicon antifoam	0.005 kg

Eudragit L30D was poured in 1.1 kg water under stirring to avoid foaming. 6,5 g NaOH were added and stirring was continued for further 30 minutes. A latex was obtained that was sieved through a 0,25 mm mesh sieve. Triethyl citrate, talc and antifoam agent were added, then the suspension was homogenized together with the Eudragit suspension. The tablets prepared according to example 3.2 were introduced into a vessel and sprayed with the mixture obtained as mentioned above, by employing a peristaltic pump and a Graco atomizer gun. The mixture was sprayed with a pressure of 1,5 bar and at a rate of 40 g/minute with an air capacity of 7 m<sup>3</sup>/minute at 55°C. The tablets temperature was maintained at 34°C.

#### 15 Example 7

In man evaluation of pharmacokinetic and pharmacodynamic parameters of the oral NO-diclofenac formulation described in example 2 (sachets).

Six healthy fastened patients were administered with 75, 100 and 150 mg NO-Diclofenac sachets formulated as described in example 2.

In order to evaluate the pharmacokinetic parameters, blood samples were taken at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 32 hours after administration of the pharmaceutical formulation. The active ingredient NO-diclofenac and its metabolites diclofenac and the hydroxyderivative 4-OH-diclofenac were dosed in plasma by a LC/MS/MS method, previously validated. NO-diclofenac was not found in the samples at any dosage. The pharmacokinetic parameters of plasma levels obtained for diclofenac (D) and the 4-hydroxydiclofenac (4OH-Diclofenac, 4OH-D) are reported in Table 2.



The inhibition of COX-1/COX-2, in blood samples taken at 0.5, 1, 3, 6, 10, 24 and 32 hours after administration, was also evaluated in the same patients. The obtained results are listed in Table 3.

5

TABLE 2

	Sachets 100 mg	
	<i>D</i>	4OH- <i>D</i>
$C_{max}$ (ng/mL)	415.7	281
$T_{max}$ (h)	0.55	1.4
$t_{1/2}$ (h)	6.85	11.3
$AUC_{(0-t)}$	1097.1	2446.2
$AUC_{(0-\infty)}$	1168.5	2909.0
MRT (h)	7.31	16.1

TABLE 3: COX 1 and COX 2 inhibition

	Predose		1 h		10 h	
	ng/ml	% Inhibition	ng/ml	% Inhibition	ng/ml	% Inhibition
COX 1 (TBX2)	24.95	0	5.28	-60 %	14.03	-19 %
COX 2 (PGE2)	55.29	0	29.55	-75%	10.55	-108%

The results obtained both as pharmacokinetics and as  
10 pharmacodynamics confirm that the NO-diclofenac formulation described in example 2 has a good bioavailability in terms of plasmatic levels of diclofenac and of anti-inflammatory activity measured according to the cyclooxygenase 1 and 2 inhibition.

**Example 8**

Comparison of NO-flurbiprofen bioavailability (Formula XIX) formulated in usual gelatine capsules vs sachets and tablets.

## 5 8.1: Pharmaceutical forms

## 8.1.A) Usual tablets

NO-flurbiprofen	100 mg
Mais starch	300 mg
Avicel	40 mg
10 Talc	20 mg
Colloidal silica	5 mg
Carboxymethylcellulose	40 mg
Magnesium stearate	10 mg

The active ingredient was absorbed on starch and silica  
15 without surfactants and absorption enhancers. After absorption, the granulate was mixed with talc, magnesium stearate and carboxymethylcellulose and filled in hard gelatine capsules.

## 8.1.B) Sachets

20 Sachets have been prepared as described in example 3.1

## 8.1.C) Tablets

Tablets have been prepared as described in example 3.2

The bioavailability study has been performed on 12 healthy subjects. The subjects were administered each at three  
25 different times and in a randomized way with two 100 mg capsules, 200 mg caps and 200 mg tablets containing each NO-flurbiprofen.

Blood samples were taken after each administration at the here below listed times: 0.25, 0.50, 1, 2, 3, 4, 5, 6,  
30 8, 10, 12, 16, and 24 hours. Flurbiprofen concentration in every plasmatic sample was determined by a LC/MS/MS method.

The obtained results are reported in Figure 1, and the pharmacokinetic parameters are presented in Table 4.

The obtained results show that both sachets and tablets are non-bioequivalent in comparison with usual capsules, as they give a better absorption both in terms of  $C_{\max}$  and in terms of AUC.

5

TABLE 4

	Formulation 8.1.A (2x100 mg capsules)	Formulation 8.1. B (200 mg sachets)	Formulation 8.1.C (200 mg tablets)
$C_{\max}$ ( $\mu\text{g/mL}$ )	5.8	9.7	9.2
$T_{\max}$ (h)	3	3	3
$t_{1/2}$ (h)	21.2	8.7	10.2
AUC <sub>(0-t)</sub>	62.7	86.3	83.2

## CLAIMS

1. A pharmaceutical composition for oral administration consisting of an admixture absorbed in a solid inert carrier, said admixture comprising:

- i) one or more liquid active ingredients and
- ii) one or more surfactants and
- iii) optionally a co-surfactant and/or
- iv) optionally an absorption enhancer

10 said composition forming an oil-in-water emulsion upon contact with aqueous media such as biological fluids.

2. A pharmaceutical composition according to claim 1 wherein the admixture absorbed in the inert carrier comprises:

- i) one or more liquid active ingredients;
- ii) one or more surfactants;
- iii) an absorption enhancer

20 3. A pharmaceutical composition according to claim 1 or 2 wherein said composition forms an oil-in-water emulsion with an average droplet size of from 0.05 micron to 50 micron upon contact with aqueous media such as biological fluids.

25

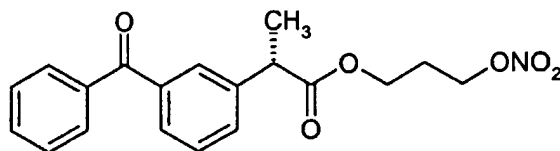
4. A pharmaceutical composition according to claim 1 or 2 wherein said composition forms an oil-in-water emulsion with an average droplet size of less than 5 micron upon contact with aqueous media such as biological fluids.

30

5. A pharmaceutical composition according to claim 1 or 2, wherein the liquid active ingredient is a NO-releasing non-steroidal anti-inflammatory drug.

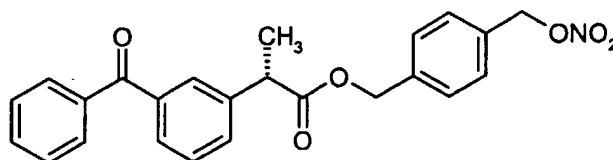
6. A pharmaceutical composition according to claim 3, wherein the NO-releasing non-steroidal anti-inflammatory drug is selected from the group consisting of:

(S)-3-benzoyl- $\alpha$ -methylbenzeneacetic acid 3-  
5 (nitrooxy)propyl ester



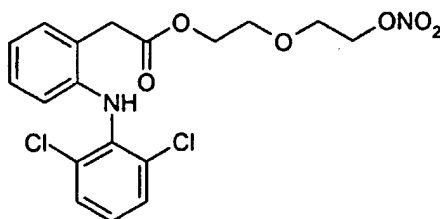
(I)

(S)-3-benzoyl- $\alpha$ -methylbenzeneacetic acid 4-  
(nitrooxymethyl)-phenylmethyl ester



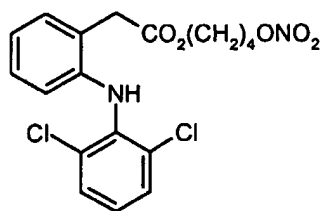
(II)

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 5-  
(nitrooxy)ethyl-oxyethyl ester



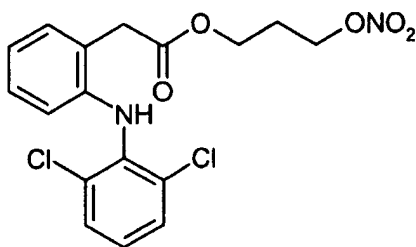
(III)

2-[(2,6-dichlorophenyl)amino]benzeneacetic acid  
4(nitrooxy)butyl ester (NO-Diclofenac)



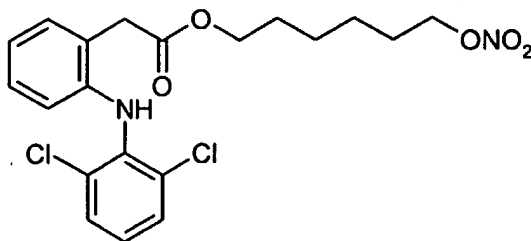
(IV)

2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid 3-  
(nitrooxy)propyl ester



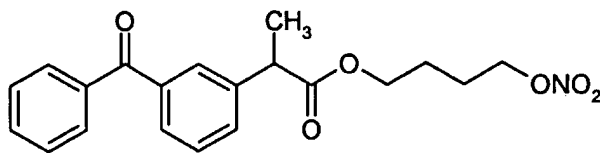
(V)

5 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 6-  
(nitrooxy)hexyl ester



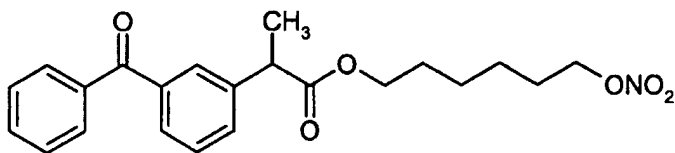
(VI)

3-benzoyl- $\alpha$ -methylbenzeneacetic acid 4-(nitrooxy)butyl  
10 ester



(VII)

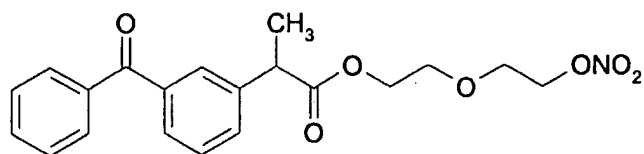
3-benzoyl- $\alpha$ -methylbenzeneacetic acid 6-(nitrooxy)hexyl  
ester



15

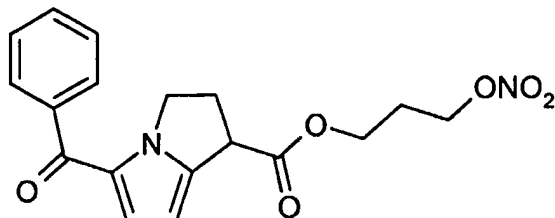
(VIII)

3-benzoyl- $\alpha$ -methylbenzeneacetic acid 5-  
(nitrooxy)ethoxyethyl ester



(IX)

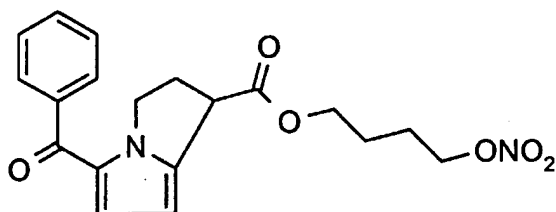
5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 3-(nitrooxy)propyl ester



5

(X)

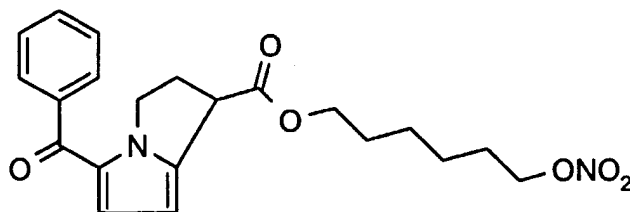
5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-(nitrooxy)butyl ester



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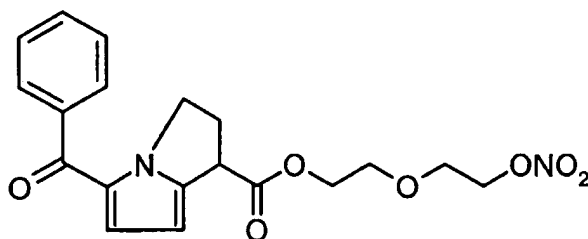
(XI)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 6-(nitrooxy)hexyl ester



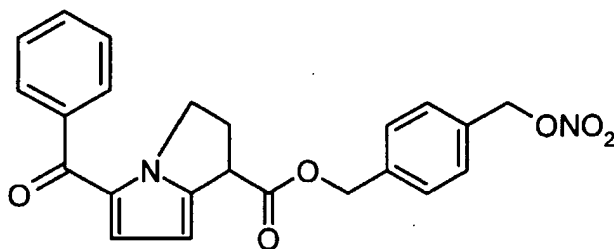
(XII)

15 5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 5-(nitrooxy)-ethyloxyethyl ester



(XIII)

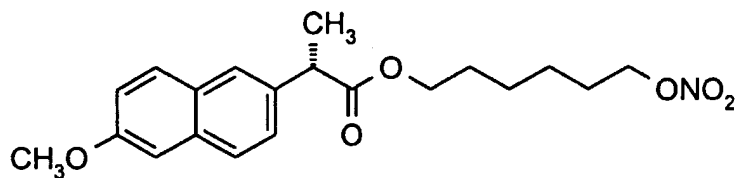
5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-(nitrooxymethyl)-phenylmethyl ester



5

(XIV)

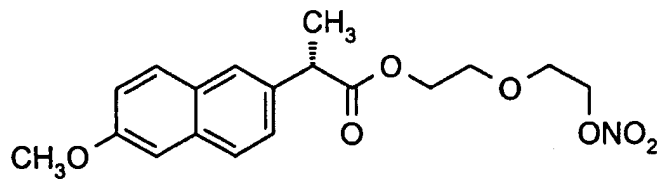
(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 4-(nitrooxy)hexyl ester



10

(XV)

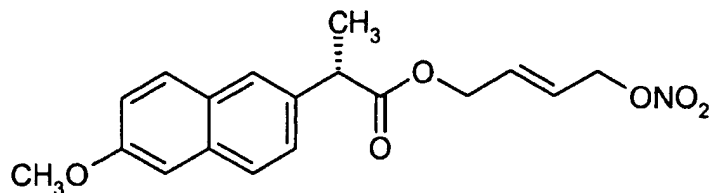
(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 4-(nitrooxy)ethyl-oxyethyl ester



(XVI)

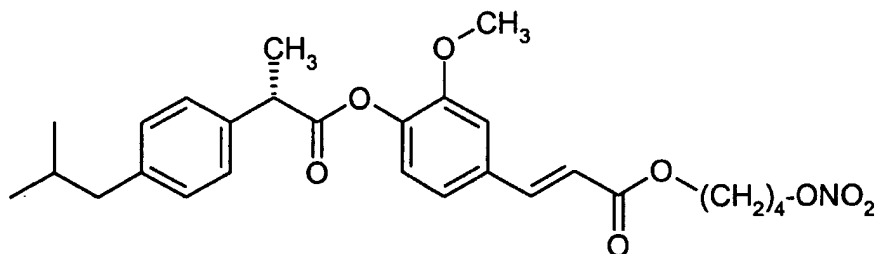
15 (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid 4-nitrooxy-2-butenyl ester





(XVII)

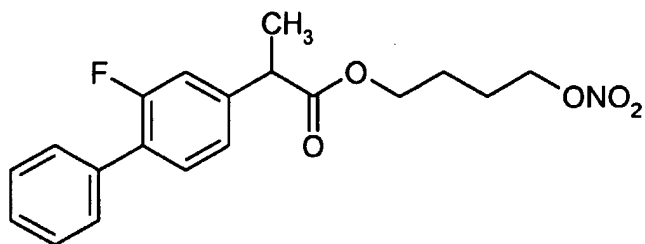
trans-3-[4-[ $\alpha$ -methyl-4-(2-methylpropyl)benzene] acetyloxy]-  
3-methoxy-phenyl]-2-propenoic acid 4-(nitrooxy)butyl ester



5

(XVIII)

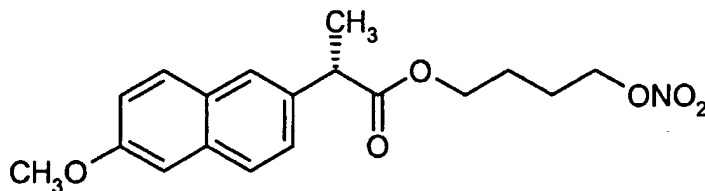
2-fluoro- $\alpha$ -methyl[1,1'-biphenyl]-4-acetic acid 4-(  
(nitrooxy)butyl ester (NO-Flurbiprofen)



10

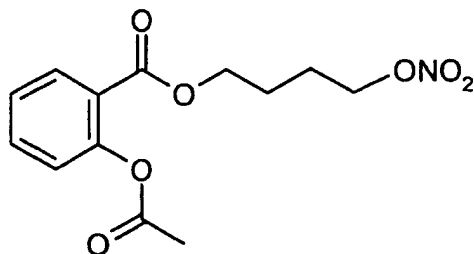
(XIX)

(S)-6-methoxy- $\alpha$ -methyl-2-naphtaleneacetic acid 4-(  
(nitrooxy)butyl ester (NO-Naproxen)



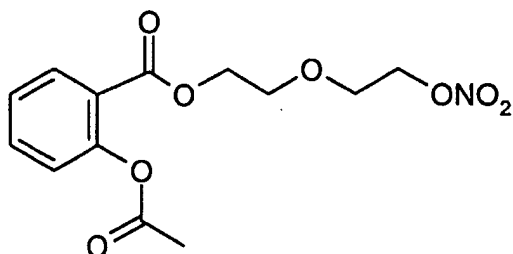
(XX)

15 2-(acetyloxy)benzoic acid 4-(nitrooxy)butyl ester



(XXI)

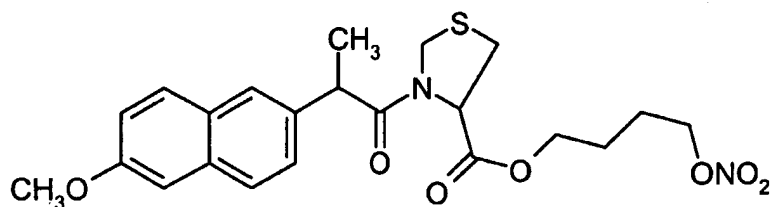
2-(acetyloxy)benzoic acid 5-(nitrooxy)ethoxyethyl ester



(XXII)

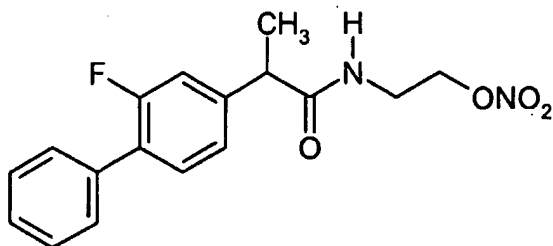
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3-(6-methoxy- $\alpha$ -methyl-2-naphtalenacetyl)-thiazolidin-4-carboxylic acid 4-(nitrooxy)butyl ester



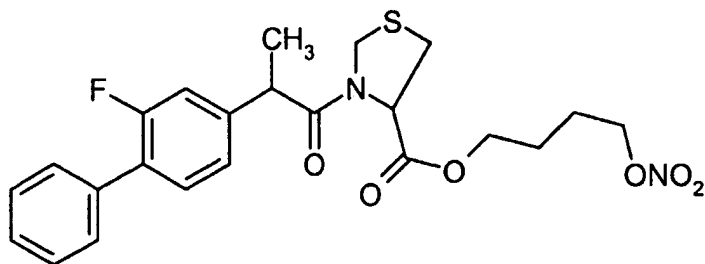
(XXIII)

10 N-(2-nitrooxyethyl)-2-fluoro- $\alpha$ -methyl[1,1'-biphenyl]-4-acetamide



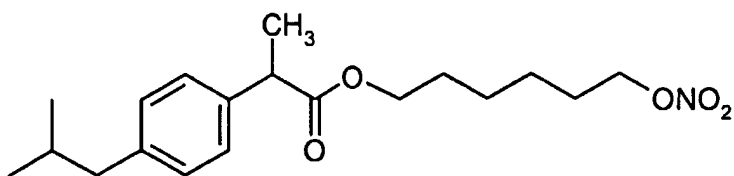
(XXIV)

15 3-[2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetyl]-thiazolidin-4-carboxylic acid 4-(nitrooxy)butyl ester



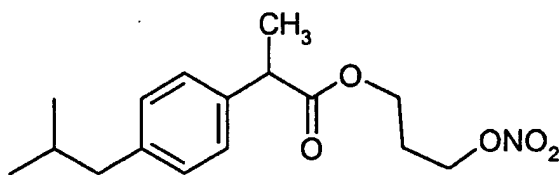
(XXV)

$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 6-(nitrooxy)hexyl ester



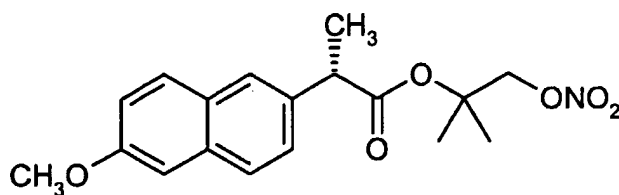
(XXVI)

$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 3-(nitrooxy)propyl ester



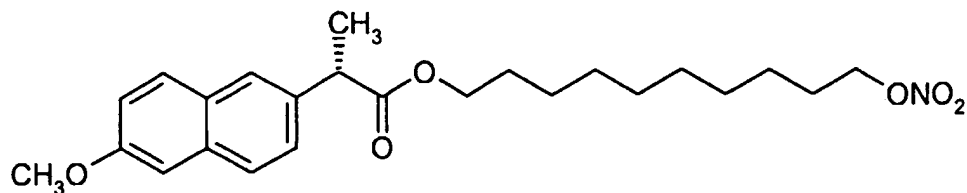
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(S)-6-methoxy- $\alpha$ -methyl-2-naphtaleneacetic acid 1-nitrooxy-2-methyl-2-propyl ester



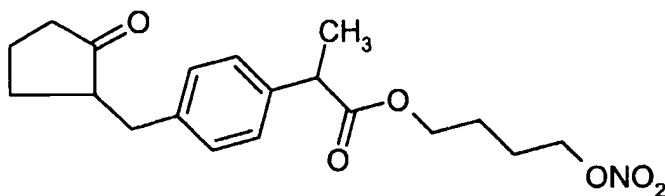
(XXVIII)

(S)-6-methoxy- $\alpha$ -methyl-2-naphtaleneacetic acid 10-(nitrooxy)decyl ester



(XXIX)

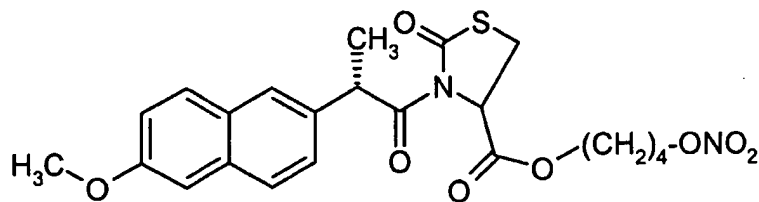
$\alpha$ -methyl-4-[(2-oxocyclopentyl)methyl]benzeneacetic acid 4-(nitrooxy)butyl ester



5

(XXX)

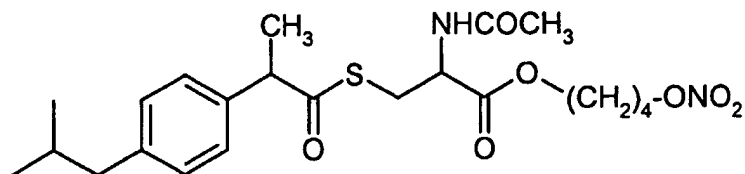
3-(6-methoxy- $\alpha$ -methyl-2-naphtalenacetyl)-R(-)-2-oxothiazolidin-4-carboxylic acid 4-(nitrooxy)butyl ester



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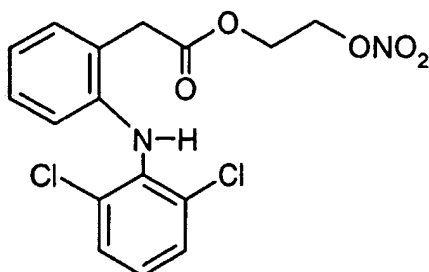
(XXXI)

(S)-N-acetyl-[ $\alpha$ -methyl-4-(2-methylpropyl)benzeneacetyl]-cysteine 4-(nitrooxy)butyl ester



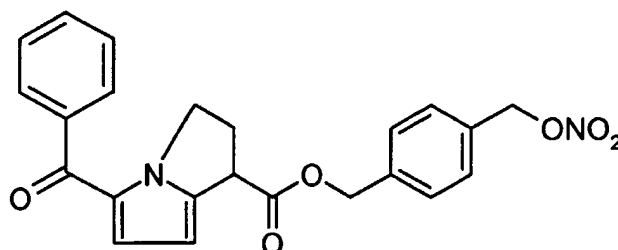
(XXXII)

15 2-[2,6-dichlorophenyl)amino]benzeneacetic acid 2-(nitrooxy)ethyl ester



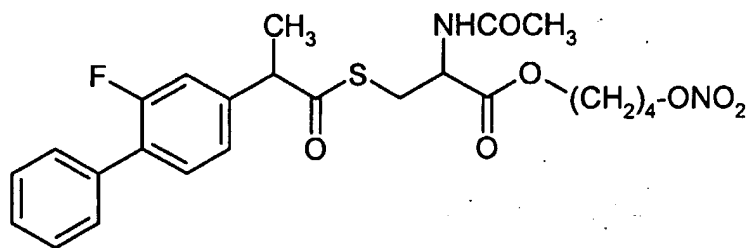
(XXXIII)

5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid 4-(nitrooxymethyl)-phenylmethyl ester



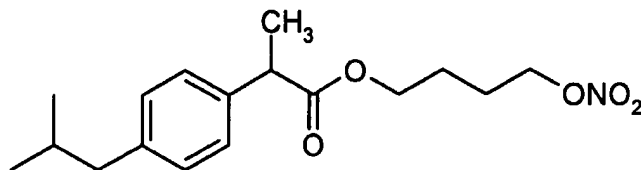
(XXXIV)

(S)-N-acetyl-[2-fluoro- $\alpha$ -methyl(1,1'-biphenyl)-4-acetyl]cysteine 4-(nitrooxy)butyl ester



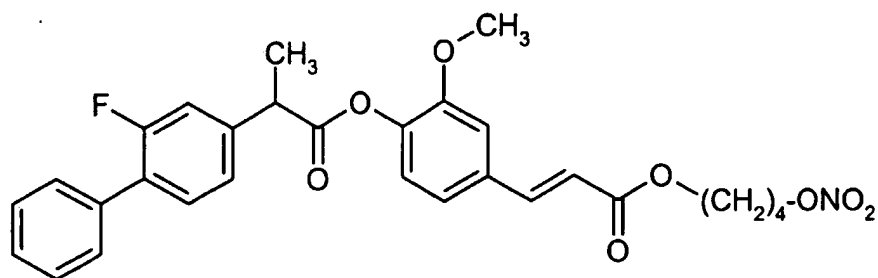
(XXXV)

$\alpha$ -methyl-4-(2-methylpropyl)benzeneacetic acid 4-(nitrooxy)butyl ester



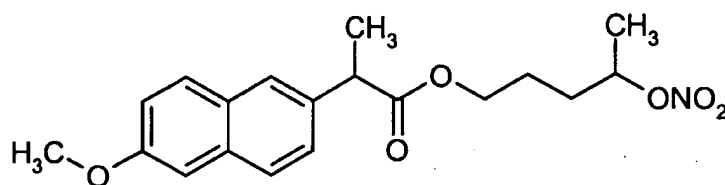
(XXXVI)

trans-3-[4-[2-fluoro- $\alpha$ -methyl(1,1'-biphenyl)-4-acetyloxy]-3-methoxy-phenyl]-2-propenoic acid 4-(nitrooxy)butyl ester



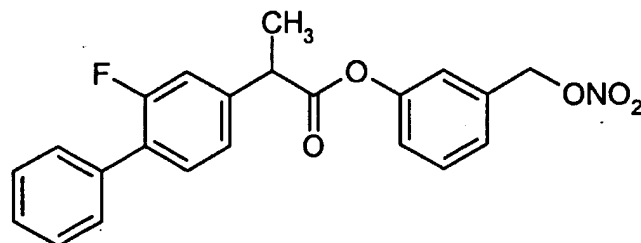
(XXXVII)

(S)-6-methoxy- $\alpha$ -methyl-2-naphthaleneacetic acid 4-(nitrooxy)-4-methylbutyl ester 4-



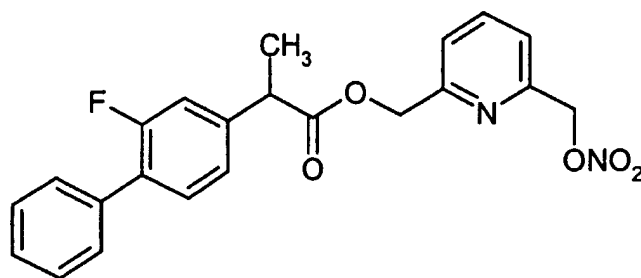
(XXXVIII)

2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 3-(nitrooxymethyl)phenyl ester 3-



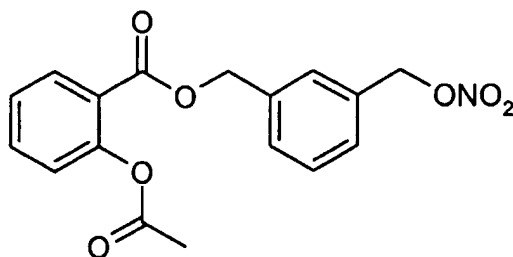
(XXXIX)

2-fluoro- $\alpha$ -methyl-[1,1'-biphenyl]-4-acetic acid 6-(nitrooxymethyl)-2-methylpyridyl ester 6-



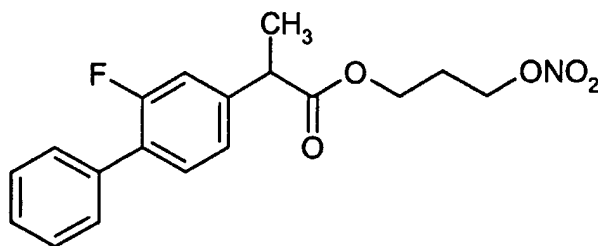
(XL)

2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)- methylphenyl ester



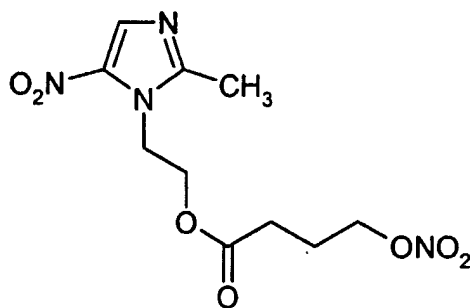
(XLI)

5 2-fluoro- $\alpha$ -methyl[1,1'-biphenyl]-4-acetic acid 3-(nitrooxy)propyl ester



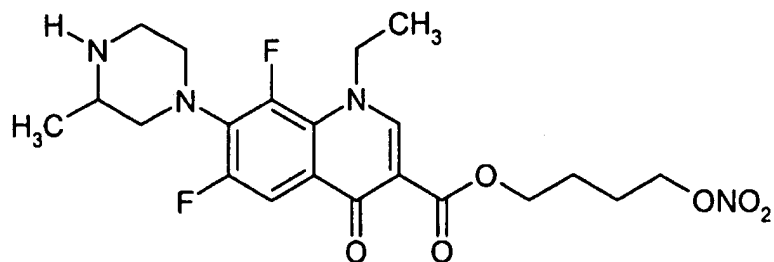
(XLII)

10 4-(nitrooxy)butanoic acid 2-methyl-5-nitroimidazole-1-ethyl ester



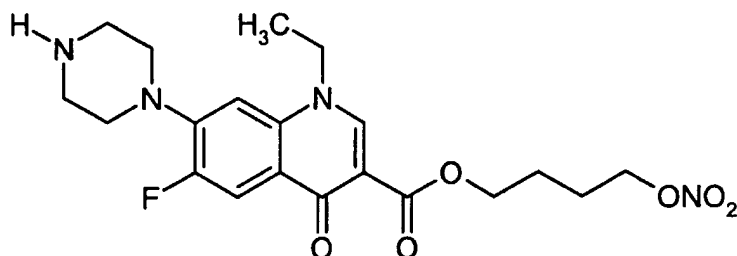
(XLIII)

1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid 4-(nitrooxy)butyl ester



(XLIV)

Norfloxacin 4-(nitrooxy)butyl ester



(XLV)

5

7. A pharmaceutical composition according to claim 1-4, wherein the liquid active ingredient is selected from the group consisting of nicotine, nitroglycerin, valproic acid, benzonatate, clofibrate, clorfeniramine, clorfenoxamine, clorfentermina and clorpromazine, liquid vitamins and mixtures thereof.

8. A pharmaceutical composition according to claim 1-7, wherein the surfactant is selected from cationic, anionic and non ionic surfactant such as alkaline soaps, organic amines soaps, sulphuric esters, alkyl aryl sulfonate, polyethylene glycol esters and ethers, polysorbates.

20

9. A pharmaceutical composition according to claim 8 wherein the surfactant is selected from the group consisting of sodium stearate, potassium stearate, sodium lauryl sulfate, sodium monolauryl glycerosulfate,



benzalkonium chloride, cetyltrimethylammonium bromide, cetrimide, Arlacel, Tween, Capmul, Cremophor, Labrafac, Labrafil and Labrasol or mixtures thereof.

5 10. A pharmaceutical composition according to anyone of the preceding claims, wherein the co-surfactant is selected from straight or branched chain alcohols, preferably C<sub>1</sub>-C<sub>6</sub> alcohols, such as ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, isobutyl alcohol, and polyols such  
10 as glycerol, ethylene glycol, propylene glycol, isopropylene glycol, butylene glycol, isobutylene glycol.

11. A pharmaceutical composition according to anyone of the preceding claims, wherein the absorption enhancer is  
15 selected from polysorbates, sorbitan esters, dioctyl sodium sulfosuccinate, ethoxy diglycol, ethoxylated nonyl phenols, polyethylene laurylether, phospholipid derivatives, fatty acids esters, biliary acids derivatives, aprotic solvents such as dimethyl sulfoxide, dimethylformamide,  
20 dimethylacetamide and 2-pyrrolidone.

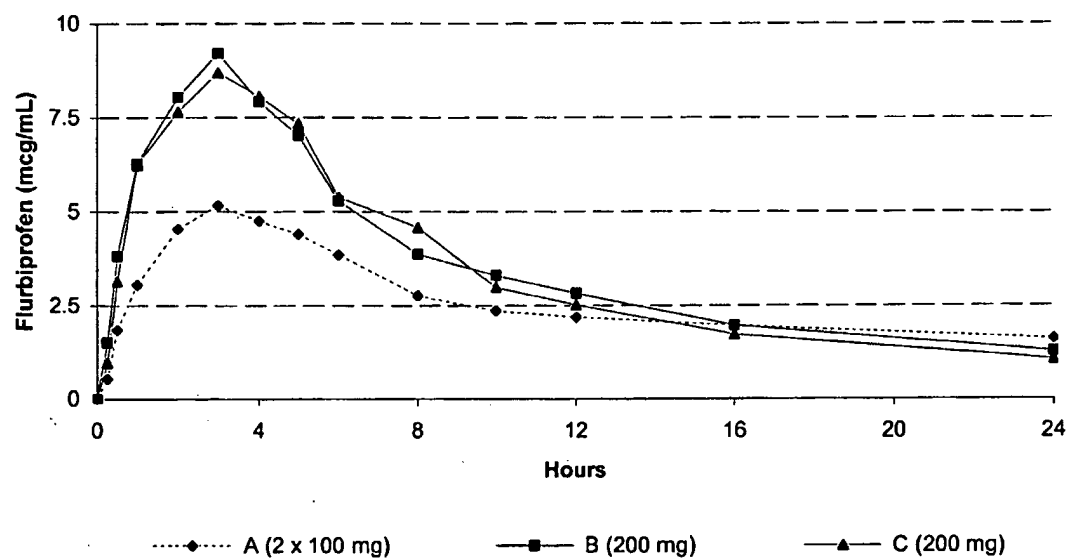
12. A pharmaceutical composition according to anyone of the preceding claims, wherein the inert solid carrier is selected from the group consisting of clays such bentonite,  
25 kaolin, silica derivatives such as Aerosil, Carbosil, cellulose derivatives such as Avicel, silicates such as magnesium trisilicate, talc, earth-alkaline metal hydroxides such as magnesium and aluminium hydroxide, starch, sugars and cyclodextrines.

30

13. A pharmaceutical composition according to claim 9 wherein the inert solid carrier is silica.

14. A pharmaceutical composition according to anyone of the preceding claims, wherein the ratio of active ingredient:surfactant is of from 1:0.1 to 1:10.
- 5 15. A pharmaceutical composition according to anyone of the preceding claims, wherein the ratio of co-surfactant:surfactant is of from 1:0.1 to 1:5.
16. A pharmaceutical composition according to anyone of  
10 the preceding claims, wherein the ratio of absorption enhancer:surfactant is of from 1:0.1 to 1:10.
17. A pharmaceutical composition according to anyone of the preceding claims, wherein the ratio of admixture :  
15 solid carrier is of from 1:20 to 10:1, preferably of 1:2 to 2:1.
18. A pharmaceutical composition according to anyone of the preceding claims in form of tablets, coated tablets,  
20 sachets and capsules.

FIGURE 1



## INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 03/06496

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/107 A61K31/216 A61K31/235 A61K31/407 A61K31/426  
 A61K31/44 A61K31/4164 A61K31/4709

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 66087 A (ASTRAZENECA AB) 13 September 2001 (2001-09-13) cited in the application claims; examples -----	1,2,5,6, 8-10,18
A	WO 01 66088 A (ASTRAZENECA AB) 13 September 2001 (2001-09-13) cited in the application examples 1-15, 18-20; claims 1-5, 12-37 -----	1,2,5,6, 8-10,18
A	WO 00 61537 A (NICOX SA) 19 October 2000 (2000-10-19) cited in the application example 6 -----	1,5,6

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

14 November 2003

Date of mailing of the international search report

27/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
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Authorized officer

Van Amsterdam, L

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/06496

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 7  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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Continuation of Box I.2

Claims Nos.: 7

Present claim 1 relates to an extremely large number of possible pharmaceutical compositions. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been guided by those parts of the application which do appear to be sufficiently clear. The search has related to pharmaceutical compositions according to claim 1, wherein the liquid active ingredient is a NO-releasing non-steroidal anti-inflammatory drug (see claim 5).

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06496

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0166087 A	13-09-2001	AU 3787501 A	17-09-2001
		BR 0109012 A	03-06-2003
		CA 2401857 A1	13-09-2001
		CN 1416336 T	07-05-2003
		CZ 20023006 A3	12-02-2003
		EP 1267831 A1	02-01-2003
		HU 0300539 A2	28-07-2003
		JP 2003525893 T	02-09-2003
		NO 20024194 A	03-09-2002
		WO 0166087 A1	13-09-2001
		SK 12582002 A3	01-04-2003
		US 2003077303 A1	24-04-2003
WO 0166088 A	13-09-2001	AU 3787601 A	17-09-2001
		BR 0109014 A	03-06-2003
		CA 2401498 A1	13-09-2001
		CN 1416335 T	07-05-2003
		CZ 20023005 A3	12-02-2003
		EP 1267832 A1	02-01-2003
		HU 0300882 A2	29-09-2003
		JP 2003525894 T	02-09-2003
		NO 20024272 A	05-11-2002
		WO 0166088 A1	13-09-2001
		SK 12572002 A3	02-05-2003
		US 2003161846 A1	28-08-2003
WO 0061537 A	19-10-2000	IT MI990753 A1	13-10-2000
		AU 4400100 A	14-11-2000
		BR 0009702 A	08-01-2002
		CA 2370412 A1	19-10-2000
		CN 1354740 T	19-06-2002
		WO 0061537 A2	19-10-2000
		EP 1169294 A2	09-01-2002
		HU 0203378 A2	28-01-2003
		JP 2002541233 T	03-12-2002
		NO 20014927 A	13-12-2001
		PL 350777 A1	10-02-2003